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Dr. Jill 00:12

Welcome to Resiliency Radio with Dr. Jill, your go-to podcast for the most cutting-edge insights in functional and integrative medicine. I'm Dr. Jill, and with me today is a special guest, Colleen. We're going to dive into gut health like you've never heard it before. I'm going to introduce her in just a second, but I just want to give a background because this is special.

Dr. Jill 00:32

We were just talking before we got on the recording. For 20 years, I have been teaching doctors about gut health and the microbiome and how critical this is for all aspects of our health, so you've heard me talk about this before. And one of the things—if you're a physician, you've probably heard me, but if you're not, you maybe don't know this—I was telling Colleen here is that I've been saying that if anyone could ever come up with a probiotic with Akkermansia, this would be such a game changer. Well, guess what? Today, we are going to talk with the founder and CEO of a company called Pendulum, which has found a way to bring this to the public. And I will say that there are not many times in my podcast or career that I've been so excited to talk about something that I feel will change the landscape of healthcare. So stay tuned; you're in for a real treat.

Dr. Jill 01:20

Let me introduce our guest, and then we'll get on with the show. Colleen Cutcliffe, Ph.D., is a microbiome scientist and the CEO and co-founder of Pendulum, a company that creates microbiome products. Dr. Cutcliffe received her Ph.D. in biochemistry and molecular biology from Johns Hopkins University and her bachelor of arts in biochemistry from Wellesley College. She has over 15 years of experience leading and managing biology teams in academia, pharmaceuticals, and biotechnology. Prior to starting Pendulum, she was a senior manager of biology at Pacific Biosciences and a scientist at Elan Pharmaceuticals. Welcome, Colleen! Thanks for coming on the show!

Colleen Cutcliffe 01:58

Thanks so much for having me!

Dr. Jill 01:59

I love to start with [one's] story. We talked briefly, but I would love for our audience to hear your background. How did you get into this? And how did you discover that this was a worthy pursuit in finding out how to create a probiotic with Akkermansia?

Colleen Cutcliffe 02:16

We started this company about 10 years ago. At that time, the microbiome was just in an emerging academic space, which is confusing for a lot of people because things like probiotics and yogurts have been around for a long time. Microbiome science is the study of all of these different microorganisms that have been enabled by DNA sequencing technologies. If you've kept track of DNA sequencing, [you'd know] that [it] became affordable and usable in the early 2000s. That's when the American Gut Project was run, where we could look at all these different people and their microbiomes. What we discovered was that gut health and probiotics have a lot more potential than just helping you with an upset stomach. It's at the core of all of the systems in your body.

Colleen Cutcliffe 03:01

As a scientist and somebody who was working for a DNA sequencing company, that fascinated me. Could we bring a whole new category of products, next-generation probiotics, that could target diseases and really help people improve their health beyond the traditional GI issues? And then, on a personal level, I wanted to be able to understand how we could help people who are lower or deficient in these strains because my first daughter was born a preemie. She spent the first month of her life in the ICN, receiving multiple doses of antibiotics. We know that antibiotics completely decimate your microbiome. I felt like there was this very personal reason to also want to be able to figure out what strains are important and how we can replenish our microbiome to set my family up for future health success. So we just started the company, hoping we could find something interesting.

Dr. Jill 03:56

Wow. And you did, clearly. Like I said, I don't know when I've been so excited about a company and a product because I've been waiting for you, and I didn't even know.

Colleen Cutcliffe 04:06

And I didn't know you were waiting. You've known so much about this field even before I joined it, which I think is pretty awesome.

Dr. Jill 04:13

Yes. Often with the greatest entrepreneurs and the greatest people who make changes in medicine, life, and sciences, there is this piece of ourselves that's our family, ourselves, or someone we love who's suffered at the hands of whatever issue. We're like: "How can we solve this problem?" I love that you come at it from a very sweet place with your daughter and [that you focused on] how to optimize your whole family's microbiome.

Dr. Jill 04:45

I had breast cancer at 25 and Crohn's at 26. So I had a definite interest, selfishly, in my microbiome. And I remember years and years ago, finding a spore probiotic at first and thinking, "Okay, there's something different here." But then, as I dove into the research, I found, "Oh, there are these keystone strains." So I'm going to let you run with that and say: What is a keystone strain? Why are they so critical? And then we'll dive into why it's so hard to create Akkermansia in a probiotic.

Colleen Cutcliffe 05:10

The microbiome is an ecosystem. We think about it like a garden. There are lots of different components. They feed each other, they collaborate, and they need each other to survive. But within this ecosystem, it turns out there are certain strains that have an outsized role compared to the others, and they've started to become called keystone strains. Akkermansia has emerged as one of these keystone strains. I would say that initially, one of the reasons people got excited about it was because it was the only strain—and to date, it's still the only strain that we know of—that is responsible for regulating the mucin layer.

Colleen Cutcliffe 05:48

When we talk about having a strong gut lining and making sure you don't have a leaky gut, the core of that is making sure that you have a good mucin layer. It's basically the glue that holds everything together. Akkermansia is responsible for maintaining that glue. When you are low in that glue and low in Akkermansia, all of a sudden you have this gut barrier integrity problem, and you don't have the strongest gut lining that you could have. That's related to all these other diseases.

Colleen Cutcliffe 06:16

The first super interesting thing about Akkermansia is that it's the only strain that we know of that can regulate the mucin layer. That's important for the gut lining. But then the second thing that got discovered about it was that when you look at healthy people versus people with various diseases, you start to see this pattern emerge: All of these different people with diseases appear to be low or are entirely missing Akkermansia. That ranges from things like obesity and type 2 diabetes to people with GI issues, neurological issues, and immune deficiencies. All of a sudden, you're starting to realize that this strain is depleted across all these different diseases; it must be doing something fundamental. Over the last decade, there's been a ton of research to unlock: What is this strain doing? And why is it so fundamental to our health? So it is the keystone strain that we know of right now.

Dr. Jill 07:05

You've just done a great job with the overview of why this is so important. And I'll just tell you, clinically, that when I'm testing patients—which I've been doing with PCR so that we know the strains in the gut and in the stool—I'm always like, "Oh no!" when I see one with nondetectable levels of Akkermansia. Just like you said, it's one of those clues to me that, number one, they're probably having some trouble with the mucosal barrier, maybe even SIgA or the mucosal immune system. Before this, I didn't have an Akkermansia strain to give them. I'd love to hear your research, but for the typical strains, I don't see a change in Akkermansia or keystone strains with our other probiotics. Maybe let's talk about that because I was amazed when I looked at the research about how little research there is about things like Lactobacillus and Bifidobacterium. Tell us about why that might be [the case] in the industry.

Colleen Cutcliffe 07:59

First of all, most of the probiotics out there, if you start looking at the labels on the shelves, are Lactobacillus and Bifidobacterium strains. They became the strains out there because they were easy to culture and grow. I think that all of us have always believed that gut health is important. These are the strains that were able to be manufactured and grown, so that's what's out there. And I should say that many people experience benefits from taking those strains. But actually, the science underlying them and the clinical trials behind them are relatively sparse, and there's a lot of conflicting evidence. In fact, the AGA came out with a statement saying that

probiotics don't help with IBS specifically. I think people were taken aback by that. But it's because the data is not strong enough to support protocols to include them.

Dr. Jill 09:01

I've heard you talk about this before, but I think some of the post-biotics—like butyric acid, which is a short-chain fatty acid produced by some of these good guys—may be some of the reasons why there's conflicting [evidence]. Do you have any thoughts on how the short-chain fatty acids in the post-biotics might be playing into the data about fermented foods?—because that's much more of a big picture than just one strain of probiotic.

Colleen Cutcliffe 09:29

A quick definition of terms: The prebiotics are the foods that feed the probiotics. The probiotics are the bacteria. We think prebiotics are like fibers, polyphenols, and things like that. Those feed our bacterial strains and those are the probiotics. What these probiotics do is generate these post-biotics. You named a few of the ones that we know well—the short-chain fatty acids [such as] acetate, butyrate, and propionate. These things that they're spitting out also have a lot of health benefits. There've been a ton of animal studies showing that those post-biotics, particularly butyrate, are incredibly important for human health.

Colleen Cutcliffe 10:07

One of the challenges has been that we've been able to help so many animals with their GI issues and even metabolic issues, but that hasn't translated into humans. I think it boils down to a delivery problem. These are small molecules that are absorbed all along the way. You're asking to ingest something and hopefully it gets to where it needs to get to. I always say this is like if I were going to give you a million dollars, would you rather I put it into a suitcase, knock on your door, and hand you the suitcase, or would you rather [that] I [would have] called you and said: "Hey, I just dispersed it all over Highway 101. You can go pick it up there." Of course, you would rather have the first, because if I put it all over Highway 101, everyone would pull over and grab your money. And that's kind of what's happening when you take a butyrate pill; all the colonic cells use butyrate as their primary source of energy. While the butyrate is trying to get to the receptor you wanted to get to, all these cells are basically absorbing it, so it never gets to the target.

Colleen Cutcliffe 11:03

The delivery of those short-chain fatty acids via the probiotics is a much better way because the strain will go and live where it's supposed to be producing that postbiotic, and then it can be delivered exactly to the receptor that it's supposed to be delivered to. Foods are another great way to deliver them, too, because your foods are part of your natural system, which knows how to digest them and get them to the right location. That's all part of: How do you deliver the goods to where they need to get to?

Dr. Jill 11:29

What a great analogy, because that makes a lot of sense. I feel like clinically we're using a lot of things, and sometimes we don't have all the evidence, or the evidence doesn't support what we're claiming in clinical practice. This is where a company like yours, which is bringing out the data, [comes into play]. Before we go into one of the products that is used to treat and decrease A1C and diabetes, I want to talk about Akkermansia because some things make it very difficult and [may be the reason] why I hadn't seen it for years and years. Tell us about this anaerobe. And what is the difficulty with creating it in pill form?

Colleen Cutcliffe 12:06

Sure. I said this to you earlier: I hadn't realized how many people were excited about Akkermansia when we got excited about it. And to your point, there have been a lot of publications showing this important role and a lot of animal studies showing that there is potential benefit. But it turns out that because it's so special and unique, it's hard to grow. It lives in the mucin layer in your gut. In that part of the gut, there's no oxygen. What you're doing is trying to recreate this thing outside of the human body, where it's housed in the middle of a mucin layer with no oxygen around it. And we obviously have a ton of oxygen in the air around us.

Colleen Cutcliffe 12:55

Usually, when you grow bacterial strains, you grow them in media. They're not embedded in a mucin layer in some three-dimensional structure. It turns out to be an incredibly hard strain to grow and maintain its viability, and then, after you're able to grow and maintain its viability, to deliver it to a person and have it then be able to grow inside that person. To be fair, I don't think that I even appreciated how hard this was going to be when we started it. But I think that once we've unlocked the ability to grow this strain and were able to show that we could deliver it and

that it could have all these benefits that we all believe that it might have, it has been incredibly rewarding to be able to see how many people are benefiting from it.

Dr. Jill (pre-recording) 13:39

Hey, everybody. I just stopped by to let you know that my new book, *Unexpected: Finding Resilience through Functional Medicine, Science, and Faith*, is now available for order wherever you purchase books. In this book, I share my own journey of overcoming a life-threatening illness and the tools, tips, tricks, hope, and resilience I found along the way. This book includes practical advice for things like cancer and Crohn's disease and other autoimmune conditions, infections like Lyme or Epstein-Barr, and mold- and biotoxin-related illnesses. What I really hope is that as you read this book, you find transformational wisdom for health and healing. If you want to get your own copy, stop by ReadUnexpected.com. There, you can also collect your free bonuses. So grab your copy today and begin your own transformational journey through functional medicine and finding resilience.

Dr. Jill 14:36

Yes. As we talked about before, I'm starting to use your probiotics in clinical practice, and I've seen some amazing results, so I can vouch for that. In the short time I've been using them, it's really, really good stuff. It's interesting. I love that you said that. I was going to ask you: Before, if you had known what you know now, would you still have pursued this? Either way, it sounds pretty amazing what you've done, because you had to raise massive funds to just create a specialized lab to grow this, right?

Colleen Cutcliffe 15:05

Absolutely. Honestly, it's a question you should probably ask my investors: If they had known... I think we all thought: "We'll just grow these strains, and then we'll do these studies, and it'll be fine." It's taken a lot of investment dollars. One of the things that we've been lucky with is the kind of investors that have gotten behind us. These are not people who are trying to figure out how to make a quick buck; "What's the quick turnaround?" We've never had discussions about "how fast you are going to exit this company for me." What they got behind was our mission and our vision: That there's a new paradigm of health through the microbiome, and we can create products and create a company that is going to capitalize on that paradigm shift. And we're going to have the support not only of individuals, the

consumers who are going to use the product, but also of physicians and healthcare professionals—the people who understand holistically how disease and health should be tackled.

Colleen Cutcliffe 15:58

That's a big vision. You want to change the way we approach health with natural products through the microbiome. It has taken a lot of money. We've raised about \$150 million to build this company out. It's been a labor of love. Like I said, at the end of the day, getting to hear your story and other people's stories about the benefits they get—that's why we started the company—feels good.

Dr. Jill 16:21

Yes. Like I said, I'm a huge supporter because I love what you're doing. And I love that your background was in pharmaceuticals because, to get a new way of doing medicine, we have to take some of the industry and shift it into these things. Maybe it's a fish oil, a super-unique probiotic, or whatever. I think that the interaction with the immune system and these new, more natural molecules are much more important than just a chemical. The old school may be like a sledgehammer. A lot of these chemicals, old medicines, are such sledgehammers, whereas this is working with your system in a much more cohesive way.

Colleen Cutcliffe 16:55

Yes, and just to add to that, I think pharmaceutical companies do an amazing job of identifying things that have incredible efficacy. There is an incredibly high bar for demonstrating that these small molecules are working. But one of the big differences, as you're pointing out, is that because these are chemicals and they're not things that are naturally found in our body, we are disrupting a system unnaturally. You might get amazing efficacy, and these drugs do have amazing efficacy, but there are a lot of other side effects because this is something that your body isn't used to seeing. It doesn't know how to metabolize it. It can get into places it's not supposed to get into. But you get this immediate, real effect.

Colleen Cutcliffe 17:36

On the other hand, natural products are doing what you said, which is that they are enhancing your body's natural capabilities to improve health. But the downside that I think a lot of people don't love is that it takes a second. It's not going to be this immediate effect of a chemical entity. It's going to take a little while to see that

benefit. But then you're teaching your body how to fish as it were; it can keep doing it. But it's not an immediate bang.

Dr. Jill 18:04

Yes. And I love it. I feel that—as we're shifting and our environment is more toxic, our guts and immune systems are more messed up—we have to shift in our thinking. This, to me, is just a beautiful way to introduce a company like yours that's making a difference. Let's shift because you have one particular product called Glucose Control, right?

Colleen Cutcliffe 18:21

Yes.

Dr. Jill 18:22

I want to talk about the making of that product. Then I want you to tell the story of the studies that you did. You really put yourself out there, because when doing a study, it could come back with no efficacy. Take us through: How did you design that product? Why is it unique and effective? And then we can talk a little about the study and the results that you guys got from that study.

Colleen Cutcliffe 18:42

Sure. We got really interested in the gut-metabolism axis. A lot of times, when we think about our metabolism, we aren't thinking about our gut. But when you think about your food, a ton of it is getting digested by your gut. You have all these microbes that are there that help you digest your food and help you with your metabolism. What we observed was that people with metabolic syndrome—all the way to type 2 diabetes, but also pre-diabetes and obesity—were low or missing some of these strains. When you look at these strains and start to look at their functions mechanistically, it all starts to make sense. And it wasn't just our studies; it was studies across the world where people were sharing their data and you could look at it and see the same pattern emerging.

Colleen Cutcliffe 19:28

When you look at what these strains were and what they were presumably able to do, [you realize that] they can metabolize fiber into these short-chain fatty acids, which is the way that you naturally stimulate GLP-1 production. It became clear to us: We know that a high-fiber diet can help you with your glucose control. And we

certainly know that things like GLP-1 and insulin can help you with your glucose control. But this middle part, this microbiome that is metabolizing that fiber and stimulating these small molecules—nobody knew what those were. And these are the things that were missing in people.

Colleen Cutcliffe 20:04

The theory was pretty straightforward. What if we could give them back to people? Could we enable them to do this digestion and metabolism better? And would we be able to see that in terms of lowered A1C and lowered blood glucose spikes? That was the premise of the product. We started with a list of about 40 different strains, and then we had to go figure out how to grow them. From a very practical standpoint—we're a startup company—there were three of us doing this in an incubator lab alongside a bunch of other startup companies with very little money. We had to make tough choices early on. Which ones are able to grow? Which ones do we believe in and are going to put the effort into helping to grow? How many of these things are redundant? Maybe we don't need all of them; we just need one. So there was a lot of that going on until we got it down to five strains in this formulation, which do this multi-step reaction of metabolizing fiber and butyrate. Of course, Akkermansia was part of that formulation as well. And then we were off to the races to do preclinical trials and then clinical trials.

Dr. Jill 21:09

So you looked at the data, took all these strains, and said, "What's the most likely to benefit?" and got it down to this narrow [selection]. I'd love to talk about those species. But Akkermansia was just one of those. It wasn't necessarily that your company said, "We know the power of Akkermansia; we're going to make that in the lab," right?

Colleen Cutcliffe 21:24

No. And the crazy thing is that we had no idea. There's been data that's come out subsequently that shows how Akkermansia is able to stimulate L-cells to secrete GLP-1. We were like: "This thing probably does something with the mucin. It's low and we want to give it back." We had no idea, transparently. We had [inaudible].

Dr. Jill 21:46

It's like you stumbled upon the goal. I'm like, 'Wow!' because that has been more of a cool story. Not accidental because, clearly, you did the research, but it wasn't like a preplanned "I'm going to go after Akkermansia," which I love. I love that. Tell us

how this works together, because there's a mechanism behind it. And I want to just stop for those of you listening. If you're a doctor, you know what GLP-1 is. If you're a patient on Saxenda, Wegovy, liraglutide, or any of these drugs, you know what this is. These are the weight-loss drugs that are taking the nation by storm. But I want to just emphasize that we're talking about how our body naturally makes this peptide, GLP-1. It helps us use less insulin with the bolus [insulin] and metabolically be more healthy, basically reversing the process of diabetes. And you're saying that this probiotic combination has the potential to increase levels naturally.

Colleen Cutcliffe 22:39

Yes. And just to take a moment to differentiate [between] the GLP-1 analogs and your body's natural GLP-1, when you take these drugs, you're injecting directly into your bloodstream this GLP-1 analog. Most of these are sort of time-released, so it's maintaining your GLP-1 levels at high levels constantly. GLP-1 has a few known benefits: One is that it stimulates your body to secrete insulin and helps you metabolize the sugars that you've just consumed. The other is that it somehow tells your brain: We just ate, we're full, and we don't need to eat anymore. So people experience this satiety. They're not hungry anymore. They don't have that food noise and their bodies are metabolizing all the sugars that they're eating at very high levels.

Colleen Cutcliffe 23:28

Your body naturally makes GLP-1, as you said. But the way it's supposed to work is that you eat food, your microbiome digests that food, and then it tells your L-cells: We just ate food, so let's make GLP-1. After you eat, your GLP-1 levels spike in your bloodstream. It tells insulin to go metabolize all the sugar in your bloodstream and tells your brain: We're full. And then it goes back down. You're supposed to be on this cycle of GLP-1 going up and down as you eat food. The difference with the drugs is that they're keeping it at a high level all the time, so you're getting this constant hammering of this messaging. The natural way is through the food that you're eating and digestion by the microbiome.

Colleen Cutcliffe 24:10

To date, there are two strains that have ever been published that have shown that they can increase GLP-1: One is Akkermansia, and the other is a strain called Clostridium butyricum. And there's a lot of hard work, science, and data that went into this. But honestly, as with anything in life, there's also a fair amount of luck.

Those were two of the five strains that we happened to decide to put into the formulation. We know that these strains have evidence showing that they can stimulate GLP-1 production. And this is sort of the natural way that your body is supposed to do it.

Dr. Jill 24:45

Wow. Thanks for explaining that. Like I said, people are listening for those kinds of products. A lot of people are taking them. But I love the idea of getting back to nature. Again, those drugs were very successful first used in diabetes, not in weight loss. They found that they had that effect. So let's talk about your formulation, the study that you did, and the amazing, surprising outcome. Maybe it is not surprising that I was pretty impressed with the data that came from this study and the preliminary work that you've done.

Colleen Cutcliffe 25:13

Thank you. The formulation has Akkermansia, which we thought was just going to be there for the mucin, although obviously it has a broader role in metabolic syndrome. Then we have what's called primary fermenters and secondary fermenters. It's just that the metabolism of fibers into butyrate and short-chain fatty acids is a multi-step reaction. We have strains that can do each of those steps in the formulation. We essentially grow each of the five strains independently, test them, and make sure that they've got the right viability. Then we combine them into a pill. Initially, the study we wanted to do was "Let's find people with type 2 diabetes" because they're all the way at one end of the spectrum of metabolic syndrome. It's hard to see improvements in somebody who's already healthy. If you want to see, "Is this thing helping with A1C and blood glucose spikes?" let's go all the way to people who've been diagnosed with type 2 diabetes.

Colleen Cutcliffe 26:12

Originally, I wanted to do the study on people who were on no medication and just had type 2 diabetes. At which point my chief medical officer said: "There's really no such thing because when someone gets diagnosed with diabetes, they walk out with a prescription for metformin at least, if not other things. Anyway, if you wanted to have something that worked, it'd have to work on top of metformin because everybody's pretty much on it." I said, "All right, fine." That was a little scary because we don't exactly understand how metformin works, honestly. There have been multiple studies showing that it might work through the gut microbiome. We

were a little bit afraid that if we had people who were on metformin, maybe they were already getting the microbiome benefits and it was going to mask what our product was doing. But he wanted to get it into people with diabetes, as they were on metformin.

Colleen Cutcliffe 27:01

So we did this trial. It was a placebo-controlled, double-blinded randomized trial. One arm was placebo, one arm was this full five-strain formulation, and then one arm was a three-strain formulation. So it was just a subset of those strains. It didn't have Akkermansia in it because, as we've discussed, Akkermansia was hard to grow. We were hoping that the subset of strains without Akkermansia would work and we wouldn't need to figure out how to scale up Akkermansia.

Dr. Jill 27:25

Oh, this is kind of funny because you thought the cheaper three-strain version... It's like, "Well, maybe this will work."

Colleen Cutcliffe 27:29

Yes. "Maybe this will be just fine." But that's not what we found. What we found was that you did need the five-strain [formulation]. The three-strain formulation had some efficacy, but the five-strain formulation demonstrated that, compared to placebo, it was able to lower A1C by 0.6 points and was able to lower blood glucose spikes by 33%. Those are pretty dramatic numbers for a probiotic. That's never been demonstrated before. And it was [inaudible].

Dr. Jill 27:58

I just want to pause. It's phenomenal. And I'm just curious: When you first got some of the preliminary data in an email or a call, how did you feel? That had to feel so good!

Colleen Cutcliffe 28:10

First of all, the whole house is banked on this one play. In some ways, you have to turn it all off and say: "Now it's a little bit in God's hands. We'll just see what happens on the other side." It was a double-blinded study, so we had no idea what people were on what product. But I will tell you, we could see the data coming in, but we just didn't know what product people were on. We would see data and be like: "Oh, this person got better. I wonder if they were on the product." Or "This

person got worse. Oh my gosh, I hope they were on the placebo." There was this constant rollercoaster every day as we started to see the data, but we were blinded. We didn't know what people were on. When we finally got the analysis back and it was clear that we were seeing these results, it was a celebration.

Colleen Cutcliffe 28:59

You rarely get the first shot on goal. We were prepared to not have seen efficacy. What we were trying to understand is, "What will we need to do to improve the formulation to get to efficacy?" We were taking stool samples. We were taking lots of measurements. We were trying to [figure out], "What would be our next step if this didn't work?" [That was our] mentality. When it worked, it brought into question whether we did want to bring this directly to consumers. So we had always said, "We want to bring these directly to consumers because it helps to enable everyone to have access to them." But when you see results like that, it does call things into question, like, "Should we go down the drug path instead?"

Dr. Jill 29:37

Especially because part of the issue here is that this costs a lot to make. Before I knew any of the data behind it, I was like, "Oh, this is going to be an expensive probiotic." But now, I'm going to be your biggest fan because I understand what went into it and understand why growing *Akkermansia* costs a lot. I want to just say that publicly because if people see this and are like, "Oh, that's a lot," try it. Try it for a month and see if you don't see results or for two months. What was the length of the trial?

Colleen Cutcliffe 30:04

We had people on the product for 90 days, so three months. Then they did a wash-out period, so then they went off of the product for a month. All the results happened within 90 days.

Dr. Jill 30:18

Okay. I'm going to tell patients: "Give it a try. Try it for 90 days." That's a really fair assumption. Did you start to see things at 30 or 60 days? If you look back at the data, could you see patterns before that? Or would you recommend that if people want to see a change, they try it for a minimum of 90 days?

Colleen Cutcliffe 30:33

As you know, it depends on the person. If you're extremely low in *Akkermansia*, you

might see a benefit almost immediately. We get those kinds of reports where people report that within days, they're already seeing changes in their continuous glucose monitors. But generally speaking, your A1C, first of all, takes 90 days to turn over. If you're looking for an A1C change, you have to give it at least 90 days, just because physiologically, that's how long it takes to see anything. But I would say that with continuous glucose monitors, some people see it sooner. I always tell people: "Give it at least 90 days. If you don't see anything after 90 days, then maybe the microbiome wasn't your problem." But give it at least 90 days to see something.

Dr. Jill 31:16

That's really wise. When did you get the results? How long ago was that?

Colleen Cutcliffe 31:24

Oh boy, now you're testing my memory. It was a few years ago. It was published in BMJ. And then we launched the product right on the heels of it.

Dr. Jill 31:34

Got it. We will be sure to link to that BMJ journal and, of course, your website and everything. If you are watching or listening in your car, don't worry; we'll have this all in the show notes. You don't need to take notes; I'll include all of that there. This is called Glucose Control. We're going to talk at the end [about how], if you want to get your own, you can purchase it yourself. We'll give you codes for a discount and everything.

Dr. Jill 31:57

We talked about cost. Just so people are ready, this is an expensive probiotic, but part of it is because the manufacturing is so intensive. But you also created an alternative. Tell us about that for people who may say, "I can't afford that, but I still want to try something similar." What's the alternative?

Colleen Cutcliffe 32:11

Yes. Thank you for pointing out how expensive it is to make. What I will also say about Glucose Control is that it has to be maintained cold. We are cold shipping it overnight to your home, and then you throw it in your refrigerator. So there are a lot of things about that product that are less than ideal, let's say. In fact, when we first launched it, we were losing money on every bottle we sold because it is expensive to make.

Colleen Cutcliffe 32:35

We got a lot of feedback from people saying, "Look, I can't afford \$165 a month"—that's what the membership is—"but I want to benefit from this." Or people were saying: "I don't have type 2 diabetes. I have pre-diabetes," or "Diabetes runs in my family. Do I need this full potent formulation?" And then other people are saying: "This is annoying to have to keep something in the refrigerator. I just want to keep it on my shelf." We were getting all this feedback and information from people. And then we had people who were on the product and said: "Oh my gosh, this has been a life changer for me, but I can't stay on it. I can't afford it."

Colleen Cutcliffe 33:08

What we decided to do was go back and look at the data and test out the idea of a lower dose. This happens all the time in the pharmaceutical industry, where it's a dosing game where you're trying to figure out for each person what's the right dose for them. What we found was that you could lower the dose, and for a lot of people, they would still get the same benefits. They didn't need the full clinical dose, which is for people with type 2 diabetes. We launched Metabolic Daily as a response to the feedback that we were getting. It's the same formulation, but just a lower dose. It's at the \$49 price point. It's for people who are trying to metabolize their sugars and carbs better, but they're not full-on, "I've got diabetes; I'm trying to lower my A1C."

Dr. Jill 33:53

I love that. Hopefully, in a year or so, we'll give you [an update from] my small clinic [on] what's happening and what we're using because I plan to be using this. Briefly, we talked about Akkermansia. It's grown anaerobically, which means no oxygen can get in. Everything in your lab is protecting that molecule from oxygen. But tell us briefly about: Why is it cold? How do you take that bug out of this anaerobic environment, put it in a capsule, and then get it into the body? Tell us just a little bit about that mechanism, because I'm sure that took a lot of work too.

Colleen Cutcliffe 34:22

Sure. If we can remember back to middle school biology, it all starts with a petri dish. You grow these strains on a petri dish and you pick a single colony. We're growing them in these large metal tanks. If you've ever been to a brewery or a vineyard, you've seen these big tanks where things are being fermented. Our manufacturing plant looks like that with all these big tanks. You're basically growing these strains and helping them divide in a medium that is rich with sugars,

nutrients, and amino acids. They grow and they're very happy in that anaerobic media environment. And then you want to give them that in a pill. We use centrifugation. We spin the cells down, we throw away the media, we take this cell paste, and then we freeze dry it. The freeze-drying process turns it from these live cells into lyophilized freeze-dried powder and then that powder is what can go into the pills. Once it is in powder form, they're in a dormant state, and they're not sensitive to oxygen anymore, so you can get it into a pill. You can have it in your fridge. You can have it outside of that and it's fine. It's during the growth that you have to keep all the oxygen out when it's alive and growing.

Dr. Jill 35:44

I think I heard you say before that temperature is a big deal, but moisture is an even bigger deal because that's what activates it into the active state. Is that right?

Colleen Cutcliffe 35:53

Yes. The first challenge is: How can you grow the strain? The second challenge is that I've got to give it to you and it's got to then come back alive in your gut. One of the primary ways it does that is when it gets exposed to the water and the moisture in your gut; that's what revives them and brings them back to life. Of course, in your gut microbiome, there are all the nutrients and all the things that they want and need to grow and thrive. The problem is that when it's in pill form, you don't want it to get exposed to moisture and you don't want it to come back alive and say, like: Here we are! [inaudible]. There's oxygen and they'll all die. So what we worry a lot about is keeping moisture out. We have desiccant packets like the kind you see in food to keep everything dry. And we just launched a Pro line on Fullscript, which has a desiccant lining in the bottle itself to keep the moisture out.

Dr. Jill 36:46

One thing I see in the future is that you guys, as a company and as part of this brainchild, are creating new procedures and processes for: How do we think about studying probiotics? And how do we bring them to market? I'm seeing a lot of innovation already in what you guys have done and that excites me. Great work. As we wind down here, I want to go back to practical. First of all, if people want to get this, like I said, we'll leave notes and everything as far as where to find it.

Dr. Jill 37:14

But you started with a story about your daughter and her microbiome. I want to speak to the person who may be the mother of a preemie or maybe someone who has Crohn's or colitis like I did. What would you say as far as hope with the microbiome and some of these interventions with someone who has had issues or has an illness related to the gut? Give us a little soundbite for those listening who may have suffered because of their microbiomes.

Colleen Cutcliffe 37:41

I think the short answer is that there is hope. The science is advancing incredibly quickly. There's great research going on. If the products that are out there now haven't been working for you, none of them have been targeting the microbiome. There is hope for a whole new line of therapies that are going to work. One of the things that's always been fascinating is that one of the ways in which people try to treat many of these diseases is through antibiotic treatment. The idea is that you've got these bacteria that are maybe causing inflammation so then you're just trying to kill them all off. In fact, the world that we want to live in is one where we're not killing all the bacteria, but we're giving the ones that do the important work. But that's harder to do because it's easier to just kill everything than to try to figure out: What are the beneficial microbes and how do I deliver them? But that's where we're all heading.

Colleen Cutcliffe 38:32

I would say that if you've been suffering from these chronic illnesses and feel like nothing's worked for you, try some of these next-generation probiotics and see if they can help you out. We did all of our studies on people with type 2 diabetes. We've been focused on metabolism. But with these short-chain fatty acids and butyrate and the relationship between these strains and the inflammatory and immune responses, all that data is growing. We certainly have physicians who are using these strains with their patients for things like IBD and IBS and seeing great benefits.

Dr. Jill 39:09

I love that. I love the hope that it brings. And it's interesting, I'll comment, because, like I said, before I understood the price, the why [behind] Glucose Control, and all the mechanisms behind the thoughtfulness of that product, all I knew was Akkermansia. I love it. I've been giving that Akkermansia and I've been using it in Crohn's, colitis, and IBD—in the non-metabolic patient—and seeing good results.

[inaudible] Let's just mention, too, that you do have a product called Akkermansia. Is that just plain old Akkermansia?

Colleen Cutcliffe 39:37

It is. And I'll tell you a funny story about that. As I said, we really didn't know what we had stumbled on when we found Akkermansia. We decided we wanted to grow it. But after we released Pendulum Glucose Control, we had a bunch of people calling us and saying: "I just want Akkermansia. I have to buy this whole formula. It's so expensive. I just want that one strain." We thought to ourselves: "How small is this subgroup of people that even know what Akkermansia is? This is a new strain. This has got to be a small group of educated folks and probably represents a very small percentage of the population." But we were getting so much of that request coming in that we just decided: "Let's just run an experiment. Let's make 10,000 bottles of just Akkermansia and let's see what happens." In less than 10 days, every bottle was spoken for.

Colleen Cutcliffe 40:26

We realized: "Oh my gosh, there's a market for this! Let's just start selling it." You're not alone in having been waiting for this strain to come out. Not only did that become our number one seller, but we then started to get practitioners saying: "I would like a high dose version and a low dose version because I have some patients in whom I want to replenish their Akkermansia at a high amount, and I have other patients that have sensitive GIs so I want to step them into increasing their Akkermansia levels." So we just launched these Pro versions, which have a low and high Akkermansia [count]. I certainly did not know that there was going to be demand for the product. But if you're sort of a minimalist and you're thinking, "It's just Akkermansia that I want to increase," we do offer just that single strain. We also offer a single strain of *Clostridium butyricum*. This is if you're trying to use the minimum viable product.

Dr. Jill 41:24

Wow. I just love that. I hope that I was just a tiny bit of a part of getting people excited [inaudible].

Colleen Cutcliffe 41:29

Yes, you might have been one of those.

Dr. Jill 41:31

Probably not, but it's just fun to think that. Colleen, thanks for your ingenuity, your creativity, and your willingness to put yourself out there. To start up a company like this takes a huge risk and a lot of gall. [laughter] But I'm so glad. I'm so glad you're out there doing this work. I'm so glad you brought this. Where can people find you and your company? And I think you guys have given our listeners a discount if they want to get some products.

Colleen Cutcliffe 41:57

Yes, absolutely. You can go to our website, PendulumLife.com. We have a bunch of information there too if you want to learn more about the microbiome and these strains, what they're doing, and other studies out there. That's where you can buy it. You can also buy our products on Amazon. We also sell them, if you're a practitioner, on Fullscript. I also just want to encourage people: We love to get feedback. Please ask us questions and let us know what you're experiencing. And then for your listeners to help make it a little easier to trial, we have a discount code called DrJill20. That gives you a discount off your first bottle of any of the products on membership. And if you're a practitioner, we have a different code, which is WSDrJill40. That is to enable wholesale purchases of the products. We would just love for people to trial and see how the strains might benefit their health.

Dr. Jill 42:54

Awesome. Repeat those codes and I'll be sure to put them in the notes. The code for a consumer's first purchase, 20% off, is?

Colleen Cutcliffe 43:01

DrJill20.

Dr. Jill 43:04

Okay. And the one for practitioners for their wholesale account would be?

Colleen Cutcliffe 43:06

WS—standing for wholesale—WSDrJill40.

Dr. Jill 43:11

Perfect. Okay. I just want to get those. And we'll have them in the notes if you're driving, so don't stop and take notes. Colleen, like I said, thanks again for being a

pioneer in this work. And thank you for everything. Thanks to your daughter for just being an inspiration. I love those stories because that's where the heart comes into what we do. And I'm just grateful that all of that led you to where you're at now. We are so grateful for your work!

Colleen Cutcliffe 43:33

Thank you so much for having me! And also, thank you for sharing all this information with your listeners because it is hard to know what probiotics are doing what. Your credibility and your willingness to take time to deep dive into these are super helpful. And I really appreciate your time!

Dr. Jill 43:49

Thank you so much!